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In the Supreme Court of the United States

OCTOBER TERM, 1964.

No. 701.

DR. HENRY TURKEL and UBIOTICA CORPORATION,

Petitioners,

v.

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION AND WELFARE,

Respondent.

PETITION FOR A WRIT OF CERTIORARI
To the United States Court of Appeals
For the Sixth Circuit.

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DEPARTMENT OF HEALTH, EDUCATION AND WELFARE,

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PETITION FOR A WRIT OF CERTIORARI
To the United States Court of Appeals
For the Sixth Circuit.

Petitioners pray that a Writ of Certiorari issue to review the judgment of the United States Court of Appeals for the Sixth Circuit entered in the above case on July 21, 1964.

OPINION BELOW.

The opinion of the Court of Appeals for the Sixth Circuit is reported at 334 F. 2d 844; and is printed in the Appendix hereto, *infra*, pp. 12-16.

JURISDICTION.

The judgment of the Court of Appeals was entered on July 21, 1964 (page 17, *infra*). Rehearing was denied on September 14, 1964 (page 18, *infra*). The jurisdiction of this Court is invoked under 28 U. S. C., Section 1254(1).

QUESTIONS PRESENTED.

In a suit filed under the provisions of 21 U. S. C. 355-(h), providing for a Petition to Review an order withdrawing approval of an application granting an exemption for the investigational use of a drug, the Court of Appeals for the Sixth Circuit granted the Respondent's Motion to Dismiss said Petition to Review. The Court of Appeals stated in its decision that there was no recourse available to the Petitioners to review the order of the Food and Drug Administration, issued against the Petitioners. The Court of Appeals further made a finding that a tendered record of the Food and Drug Administration could not be received by the Court for its consideration in connection with the issues presented in this cause. The questions presented are:

1. Whether the 1962 Amendments to the Food and Drug Act that the right of appeal to the United States Court of Appeals granted by 21 U. S. C., Section 355(h), applies to an order of the Secretary, Health, Education and Welfare Department, withdrawing approval of an investigational exemption granted permitting the distribution of a drug for investigational use.

2. Whether Section 262 of the Judicial Code grants jurisdiction to federal courts to review an order of the Secretary, Health, Education and Welfare Department, withdrawing approval of an investigational exemption granted permitting the distribution of a drug for investigational use.

3. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects against unreasonable and unwarranted conditions imposed by regulations adopted by a federal agency under a directive contained in an Act of Congress.

4. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects against an unreasonable and unwarranted interference in the investigational use of a drug, when all of the medical evidence available with respect to the investigational use of said drug indicates that the same is devoid of harmful effects, and beneficial to those patients being administered the same.

5. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects against a proceeding, where an investigational use exemption is withdrawn by the Food and Drug Administration, without a hearing, without confrontation, and without an opportunity to present evidence germane to the subject matter, before such time as a final order of the Food and Drug Administration is issued with respect to the termination of the investigational use exemption in existence.

6. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects duly licensed physicians against the unbridled and arbitrary use of power by the Food and Drug Administration in refusing to present and disclose reasons upon which is premised an order of termination of an existing exemption authorizing the investigational use of a drug.

7. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution requires a judicial review of proceedings conducted by a federal agency, wherein said federal agency denies a hearing, confrontation and findings before a final order is issued to Petitioners.

CONSTITUTION, STATUTES, FEDERAL RULES AND REGULATIONS INVOLVED.

Involved herein are the following: Amendment V, U. S. Constitution, set forth in the Appendix at page 18; Federal Food, Drug and Cosmetic Act, as amended, 21 U. S. C. 355, set forth in the Appendix at pp. 19-27; Regulations adopted by the Food and Drug Administration, 28 Federal Register, 170-182, 319, 5048 (21 C. F. R. 130.3), set forth in the Appendix at pages 27-48; and Rules 26 and 33 of the Federal Rules of Civil Procedure.

STATEMENT.

In 1943, Dr. Henry Turkel developed and created a certain combination of drugs and vitamins, which were then and are now commonly used as medicines, which are called the "U" Series Drugs. The purpose of the "U" Series Drugs is for the medical treatment of the condition known as mongolism, which is a recognized medical phenomenon existing in certain human beings.

Between the years 1943 and 1957, certain modifications with respect to the ingredients were made by the Petitioners; and since 1957, the ingredients have remained constant.

Since the year 1957, the "U" Series Drugs have been prescribed by the Petitioners and by many other physicians throughout the United States, and used in the treatment of hundreds of mongoloid patients, with marked results indicating that the same are a safe and effective treatment.

Prior to October, 1962, the Petitioners presented their findings to the Food and Drug Administration, and were used between 1957 and 1962 with the full knowledge of the said Food and Drug Administration.

When the existing Federal Food, Drug and Cosmetic Act was amended in October, 1962, the Petitioners there-

after filed a "Notice of Claimed Investigational Exemption for New Drug" pursuant to the provisions of the statute and certain regulations adopted by the Food and Drug Administration. On October 4, 1963, Petitioners received a notice from the Food and Drug Administration raising certain questions relative to the manufacture, composition, processing and animal testing of the "U" Series Drugs. On October 10, 1963, the information requested was furnished by the Petitioners, with the exception of technical data which was in the process of preparation by Direct Laboratories, Inc., Buffalo, New York, a pharmaceutical manufacturer licensed, supervised and inspected by the Food and Drug Administration.

On November 29, 1963, the Food and Drug Administration issued an order terminating the investigational use exemption, and decreeing that the Petitioners discontinue the administration of the "U" Series Drugs to human beings.

Upon receip of this order of the Food and Drug Administration, the Petitioners requested a hearing, which was held on December 17, 1963, at which hearing the Petitioners were denied the right to learn of the basis of the findings, or of the findings themself, of the Food and Drug Administration; Petitioners were further denied the right to interrogate the personnel of the Food and Drug Administration; further Petitioners were denied the right of apprisal of the basis of the issuance of the order by the Food and Drug Administration.

As a result of the issuance of the order by the Food and Drug Administration, in excess of 100 patients who were receiving the "U" Series Drugs as a medical treatment were denied the same, which action resulted in, and continues to result in regression of their physical condition.

The Food and Drug Administration further notified the Petitioners that if the order of November 29, 1963, was violated, that Petitioners would be prosecuted criminally.

The Food and Drug Administration refused and failed to answer requests by the Petitioners for further proceedings; and in effect, became incommunicado to the Petitioners' request for a formal hearing or for other proceedings with respect to the order of November 29, 1963.

Under and by virtue of the provisions of 21 U. S. C., Section 355(h), the Petitioners instituted a Petition to Review in the U. S. Court of Appeals for the Sixth Circuit.

Under the provisions of 21 U. S. C., Section 355(h), the Respondent, the Food and Drug Administration, tendered to the Court of Appeals the record, requesting that the same be filed "in camera" with the Court. The Court of Appeals refused to file the same, and hence at no time was the complete record before the Court of Appeals.

A Motion to Dismiss was filed by the Food and Drug Administration, which Motion was granted by the Court of Appeals, based upon their interpretation of the provisions of 21 U. S. C., Section 355(h). This interpretation stated in essence that the Petitioners have no regress or recourse from the action of the Food and Drug Administration; and further that the Due Process Clause of the Fifth Amendment has not been violated by the summary and arbitrary action of the Food and Drug Administration.

The Court of Appeals in its decision, by way of dictum, interprets the provisions of the statute and the regulations adopted pursuant thereto in such a manner as would suggest that the facts of this case were not before the Court.

The Court of Appeals in the oral argument on the Motion to Dismiss, asked the question: "Is there any protection afforded to the Petitioners in the event that the

Commissioner of the Food and Drug Administration exercises the power granted to him by the statute and the regulations in a dishonest manner?"

While the answer to this question was discussed in oral argument before the Court of Appeals, the Court completely ignored the same in its opinion and decision.

In effect, the Court held that there was no protection to the Petitioners in this case where all of the procedural requirements of due process were ignored and denied to the Petitioners by the arbitrary, unwarranted and summary action of the Food and Drug Administration.

REASONS FOR GRANTING THE WRIT.

The decision below should be reviewed because it erroneously interprets the 1962 Amendments to the Federal Food, Drug and Cosmetic Act, so as to deny the Petitioners the right of judicial review of a final order of the Food and Drug Administration.

1. This cause presents a public question high in the scale of the nation's interest in public health, and presents a compelling justification for prompt judicial resolution of the controversy over the power of the Food and Drug Administration to determine whether research and investigational use of a drug can be carried on by a physician. The issue here is whether a judicial review is available to the Petitioners, in a case where the sole interest and efforts of the Petitioners are directed toward an improvement of the public health of certain of its citizens.

The sole purpose of the Petitioners is to seek judicial review of an order of the Food and Drug Administration, which Petitioners contend was made in excess of the delegated powers of the Food and Drug Administration.

Accordingly, as this Court stated in the case of *Boire v. Greyhound Corporation*, 376 U. S. 473, where a public question is high in the scale of our national interest, there is justification for a prompt judicial review of said question. This Court followed the tenor of its pronouncement made previously in the case of *Leedom v. Kyne*, 358 U. S. 184.

2. The Court below sought to avoid the questions raised by the Petition to Review, by summarily assuming, without reference to the record in this cause, that the order of the Food and Drug Administration was not a "final order." No such assumption is justified by the record herein.

However, when the Food and Drug Administration filed the record required by the provisions of 21 U. S. C. 355(h), and attempted to place a reservation to the examination by the Court of these records, by requesting that they be filed "in camera," the Court below refused to look at the record and consider the same in the determination of whether their assumption was correct or incorrect.

Accordingly, the Court below made a determination with respect to jurisdiction by a narrow and unrealistic finding that the pertinent provisions of the statute did not apply to the facts in this case; when in truth and fact, the Court did not apprise itself of the record tendered for filing by the Food and Drug Administration; and ignored by the Court completely in this case.

3. In the interpretation of 21 U. S. C. 355(h), and other pertinent sections of the Federal Food, Drug and Cosmetic Act, the Court did not consider the obliteration of the right of the Petitioners to engage in the investigational use of a drug.

Nor did the Court consider that such interpretation of the statute was a denial of the Due Process Clause of the Fifth Amendment.

However, this Court in the case of *Leedom v. Kyne*, 358 U. S. 184, has stated at page 190 as follows:

> "Here * * * absence of jurisdiction of the federal courts would mean a sacrifice or obliteration of a right which Congress has given professional employees for there is no other means, within their control to protect and enforce that right. And 'the inference is strong that Congress intended the statutory provisions governing the general jurisdiction of those courts to control.' * * * This Court cannot lightly infer that Congress does not intend judicial protection of rights it confers against agency action taken in excess of delegated powers. Cf. *Harmon v. Brucker*, 355 U. S. 579; *Stork v. Wickard*, 321 U. S. 288; *School of Magnetic Healing v. McAnnulty*, 187 U. S. 94."

4. In the interpretation of the Federal Food, Drug and Cosmetic Act made by the Court below, the Court was not mindful of the pronouncement of this Court in the case of *American Federation of Labor v. National Labor Relations Board*, 308 U. S. 401, p. 408, where it is stated as follows:

> "* * * Administrative determinations which are not commands may for all practical purposes determine rights as effectively as a judgment of a Court, and may be re-examined by Courts under particular statutes providing for review of 'orders.' See *Rochester Telephone Corp. v. United States*, 307 U. S. 125, 130, 135, et seq.; *Federal Power Comm'n. v. Pacific Power & Light Co.*, 307 U. S. 156."

5. The Court below in its interpretation of the Federal Food, Drug and Cosmetic Act, and the Regu-

lations adopted pursuant thereto, did not consider the denial of the guarantees of the Due Process requirements of the Fifth Amendment of the U. S. Constitution.

The record shows that the procedures followed by the Food and Drug Administration in terminating the exemption violated the traditional concepts of Due Process, in that a finding was made without an opportunity to be heard, and a proceeding had in which no applicable rules of law and procedures were observed or allowed; all in direct contravention of the statements of this Court in the cases of *St. Joseph Stock Yards Co. v. United States,* 298 U. S. 38; *Rochin v. California,* 342 U. S. 165; *Yanataya v. Fisher,* 189 U. S. 86.

As this Court has stated and reaffirmed, the individual's substantial rights must be protected, where the Government is exercising the power to regulate, license and control an entire branch of business. *Cafeteria & Restaurant Workers Union, Local 473, AFL-CIO v. McElroy,* 367 U. S. 886.

The questions presented by this case are of great and recurring significance in the administration of the 1962 Amendments to the Federal Food, Drug and Cosmetic Act, and elsewhere. The serious question of the denial of the right of judicial review, and the effect of the decision below, if unreversed, on the unbridled power and authority of a federal agency, makes this case a peculiarly appropriate one for the exercise of this Court's discretionary jurisdiction.

CONCLUSION.

For the reasons set forth above, it is respectfully submitted that this Petition for a Writ of Certiorari should be granted.

LEO E. RATTAY,
Counsel for Petitioners.

APPENDIX.

OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT.

(Decided July 21, 1964.)

Before: MILLER, PHILLIPS and EDWARDS, Circuit Judges.

EDWARDS, Circuit Judge. Respondent, Food and Drug Administration, filed a motion to dismiss the appeal which petitioners, Dr. Henry Turkel and Ubiotica Corporation, initially filed in this court under Section 505(h) of the Federal Food, Drug and Cosmetic Act, 21 U. S. C. § 355-(h).

The petition sought to enjoin and vacate an order of the Commissioner of Food and Drugs terminating the investigational exemption previously allowed petitioners for investigational distribution of the "U" Series Drugs in the treatment of mongolism in children.

The motion to dismiss was based on the contention that Section 505(h) of the Act, 21 U. S. C. § 355, which grants a right of appeal to the United States Court of Appeals "for the circuit wherein such applicant resides or has his principal place of business" is not applicable "since there has been no order refusing to approve a new drug application." In view of the fact that the petition called for determination of a matter of first impression, this court set the motion to dismiss for oral argument.

The legislation under which the order complained of was issued is a direct product of the disclosure that the drug thalidomide had been responsible for the birth of many malformed infants in countries where it had been widely administered to pregnant women. Subsequent to these tragic events, Congress enacted amendments to the Food and Drug Act greatly widening the powers of the

Secretary to adopt regulations pertaining to interstate distribution and sale of new drugs. The new amendments also authorized promulgation of regulations for exempting from the new drug application requirements drugs intended solely for investigational use by experts. 21 U. S. C. § 355, as amended October 10, 1962. Public Laws 87-781, § 103(b), 76 Stat. 783, 21 U. S. C. § 355(i).

Among the important provisions of the 1962 Amendments were provisions which placed upon the applicant the burden of establishing that the drug proposed to be distributed in interstate commerce was safe for human use, and requiring testing prior to approval of such new drug application, with the power extended to the Secretary to require tests on animals.

Petitioners had been manufacturing the "U" Series Drugs and testing them on Mongoloid children under medical supervision for some eleven years prior to the adoption of the 1962 Amendments. On June 5, 1963, they filed "Notice of Claimed Investigational Exemption for a New Drug" under 21 U. S. C. § 355(i), as amended October 10, 1962.

On September 30 the Commissioner of Food and Drugs wrote petitioners notifying them of "inadequacies" in their "Notice of Claimed Investigational Exemption" for the "U" Series Drugs. Among other asserted deficiencies there were these entries: "No animal data are submitted. There is an inadequate amount of reporting of clinical data. * * * No real plan is submitted." The letter required correction of the inadequacies within ten days of receipt.

This was followed on November 26 by a letter from the Commissioner to petitioners notifying them: "The conditions of exemption have not been met, and the exemption allowing clinical testing of the drug is terminated. You

should immediately recall the drug from all clinical investigators and discontinue administering it to human beings."

Subsequent thereto an informal conference was held in the office of the Assistant Commissioner, Winton B. Rankin, on Tuesday, December 17, 1963, between representatives of the Food and Drug Administration and the petitioners at which the controversy was reviewed at some length. At this conference the position of the Commissioner was reaffirmed by the representatives of the Food and Drug Administration who were present. Petitioners thereupon filed a petition in this court to review the decision of the Food and Drug Administration terminating the investigational exemption as conveyed in the Commissioner's letter of November 26, 1963.

Prior to initiation of this petition for review, petitioners had also filed and then withdrawn a New Drug Application.

Respondent Food and Drug Administration moved to dismiss this appeal on the ground that 21 U. S. C. § 355-(h), relied upon by petitioners as establishing their right of appeal to this court, did not in fact confer jurisdiction upon this court in relation to withdrawal of an exemption for investigational distribution of a drug. Respondent asserts that said section grants a right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application.

After briefing of the question involved and oral argument thereon, this court has concluded that the government's motion to dismiss should be granted. It is our interpretation of the 1962 Amendments to the Food and Drug Act that the right of appeal to the United States Court of Appeals granted by 21 U. S. C. § 355(h) applies only to an order of the Secretary refusing or withdrawing

approval of an application for sale and distribution of a new drug. The denial of investigational exemption does not prohibit the processing of an application for distribution and sale of a new drug through the statutorily provided hearing and final administrative order called for in 21 U. S. C. § 355(b), (c), (d), (e) and (f).

Essentially, petitioners contend before us that requiring them to proceed with the New Drug Application and hearing prior to judicial review is a futile exercise, since they contend denial is a foregone conclusion. The answer to this is that by proceeding through the New Drug Application procedure and hearing, an adequate record for review will be developed in accordance with the congressional intent. The statute appears to us to contemplate appeal to the courts only after exhaustion of the administrative remedies and entry of a final administrative order.

This interpretation is strengthened by the fact that subsection (h) upon which petitioners rely is placed immediately following the subsections dealing with applications for distribution of new drugs, and immediately prior to the section providing for exemptions of drugs for research.

As bearing on congressional intent in this regard, we also note that the first sentence of subsection (i) pertains to "Exemption of drugs for research" and reads as follows:

> "The Secretary shall promulgate regulations for exempting *from the operation of the foregoing subsections of this section* drugs intended solely for investigational use by experts * * *." (Emphasis added) 21 U. S. C. § 355(i).

Subsection (h), which contains the appeal procedure, is one of the "foregoing subsections."

As bearing on the questions posed by this appeal, we also note that the Food and Drug Administration has promulgated regulations granting a prompt hearing in the

event the applicant desires to protest a rejection by them of his New Drug Application as inadequate or incomplete.

"§ 130.5 Reasons for refusing to file applications.

"(d) if an applicant disputes the finding that his application is incomplete or inadequate, he may make written request to file the application over protest. In such case, the application shall be reevaluated, and within 30 days of the date of receipt of such written request, the application shall be approved, or the applicant shall be given written notice of an opportunity for a hearing on the question whether the application is approvable." 21 C. F. R., Section 130.5(d), as revised June 20, 1963, 28 F. R. 6380.

In the event a petitioner's New Drug Application is rejected on grounds of inadequacy of human investigational data, where an investigational exemption had previously been refused, it appears that the merits of such refusal could be a proper issue at the New Drug Application hearing and thus be preserved for appellate review.

Such an interpretation of the statute and regulations appears to us also to be strongly suggested by the due process requirements of the Fifth Amendment.

We conclude that the statute upon which petitioner relies does not grant a right of appeal from withdrawal of an investigational exemption, except by appeal from subsequent denial of a New Drug Application.

The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute. *American Federation of Labor v. National Labor Relations Board*, 308 U. S. 401 (1940); *United States v. Agne*, 161 F. 2d 331 (C. A. 3, 1947).

The petition for review is dismissed.

JUDGMENT OF THE COURT OF APPEALS

(Filed July 21, 1964.)

Before: MILLER, PHILLIPS and EDWARDS, Circuit Judges.

This court having received in the above-styled matter certain documents tendered by respondent, Food and Drug Administration, for filing as the record on appeal, along with a letter from counsel for respondent claiming executive privilege in relation to said documents and requesting that the court consider them *in camera;* and

This court having instructed the Clerk of the court not to file these documents as the record on appeal under the conditions under which they were tendered; and

This petition for review having now been dismissed on motion for want of jurisdiction in this court, without court inspections of or consideration of the documents referred to,

NOW, THEREFORE, the Clerk of the United States Court of Appeals is directed forthwith to return said documents to counsel for respondent.

Approved for entry,

GEORGE EDWARDS,
Circuit Judge.

ORDER OF COURT OF APPEALS DENYING PETITION FOR REHEARING EN BANC.

(Filed September 14, 1964.)

BEFORE: WEICK, Chief Judge; MILLER, CECIL, O'SULLIVAN, PHILLIPS and EDWARDS, Circuit Judges.

The petition for rehearing en banc is hereby denied, and it is ordered that the petition for rehearing be referred to the panel of judges which heard the case.

Approved for entry,

GEORGE EDWARDS,
Circuit Judge.

ORDER OF COURT OF APPEALS DENYING PETITION FOR REHEARING.

(Filed September 14, 1964.)

BEFORE: MILLER, PHILLIPS and EDWARDS, Circuit Judges.

The petition for rehearing is hereby denied.

Approved for entry,

GEORGE EDWARDS,
Circuit Judge.

THE CONSTITUTIONAL AMENDMENT INVOLVED.

Amendment V.

No person shall * * * be deprived of life, liberty, or property, without due process of law * * *.

STATUTES AND REGULATIONS.

Federal Food, Drug, and Cosmetic Act, 21 U. S. C. 301, et seq.

21 U. S. C. 355.

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is ap-

provable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is

represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new in-

formation before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j), or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that

on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record

upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections

of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(1) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(2) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and

(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b).

Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

(j) (1) In the case of any drug for which an approval of an application filed pursuant to this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section: Provided, however, That regulations and orders issued under this subsection and under subsection (i) shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such

regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

28 Federal Register 170-182, 319, 5048.

21 C. F. R. 130.3.

(a) A shipment or other delivery of a new drug shall be exempt from Section 505(a) of the act if all the following conditions are met:

(1) The label of such drug bears the statement "Caution: New drug—Limited by Federal (or United States) law to investigational use."

(2) The person claiming the exemption has filed with the Food and Drug Administration a completed and signed "Notice of claimed investigational exemption for a new drug" in triplicate, with the following information:

Form FD 1571

Department of Health, Education, and Welfare, Food and Drug Administration

Notice of Claimed Investigational Exemption for a New Drug

Name of sponsor _____

Address _____

Name of investigational drug _____

To the Secretary of Health, Education, and Welfare,

For the Commissioner of Food and Drugs, Washington 25, D. C.

Dear Sir:

The sponsor, _____ submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 130.3 of Title 21 of the Code of Federal Regulations.

Attached hereto are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all

reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

7. A total of five copies of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug or chemically or pharmacologically related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each

investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in Section 10 of the "Notice of claimed investigational exemption for a new drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD 1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man—only animal and in vitro data are available—with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be

undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluations of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the com-

mercialization of a new drug for which an application is not approved.

Very truly yours,

(Sponsor)

Per ---

(Indicate authority)

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

(3) Each shipment or delivery is made in accordance with the commitments in the "Notice of claimed investigational exemption for a new drug."

(4) The sponsor maintains adequate records showing the investigator to whom shipped, date, quantity, and batch or code mark of each such shipment and delivery, until 2 years after a new-drug application is approved for the drug; or, if an application is not approved, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the Food and Drug Administration has been so notified. Upon the request of a scientifically trained and properly authorized employee of the Department at reasonable times, the sponsor makes the records referred to in this subparagraph and in subparagraph (2) of this paragraph available for inspection, and upon written request submits such records or copies of them to the Food and Drug Administration.

(5) The sponsor monitors the progress of the investigations and currently evaluates the evidence relating to the safety and effectiveness of the drug as it is obtained

from the investigators. Accurate progress reports of the investigations and significant findings, together with any significant changes in the informational material supplied to investigators, shall be submitted to the Food and Drug Administration at reasonable intervals, not exceeding 1 year. All reports of the investigation shall be retained until 2 years after a new-drug application is approved for the drug; or, if an application is not approved, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the Food and Drug Administration so notified. Upon request of a scientifically trained and properly authorized employee of the Department, at reasonable times, these reports shall be made available for inspection, and on written request copies of these reports shall be submitted to the Food and Drug Administration.

(6) The sponsor shall promptly investigate and report to the Food and Drug Administration and to all investigators any findings associated with use of the drug that may suggest significant hazards, contraindications, side-effects, and precautions pertinent to the safety of the drug. If the finding is alarming, it shall be reported immediately and the clinical investigation discontinued until the finding is adequately evaluated and a decision reached that it is safe to proceed.

(7) If the investigations adduce facts showing that there is substantial doubt that they may be continued safely in relation to the drug's potential therapeutic effects, the sponsor shall promptly discontinue the investigation, notify all investigators and the Food and Drug Administration, recall all stocks of the drug outstanding, and furnish the Food and Drug Administration with a full report of the reason for discontinuing the investigation. The Food and Drug Administration will be prepared to confer with the sponsor on the need to discontinue the investigation.

(8) The sponsor shall discontinue shipments or deliveries of the new drug to any investigator who has repeatedly or deliberately failed to maintain or make available his records or reports of his investigations.

(9) The sponsor shall not unduly prolong distribution of the drug for investigational use but shall submit an application for the drug pursuant to section 505(b) of the act (or give reasons for not submitting such application, or a statement that the investigation has been discontinued and the reasons therefor):

(i) With reasonable promptness after finding that the results of such investigation appear to establish the safety and effectiveness of the drug; or

(ii) Within 60 days after receipt of a written request for such an application from the Commissioner.

(10) Neither the sponsor nor any person acting for or on behalf of the sponsor shall disseminate any promotional material representing that the drug being distributed interstate for investigational use is safe or useful for the purposes for which it is under investigation. This regulation is not intended to restrict the full exchange of scientific information concerning the drug including dissemination of scientific findings in scientific or lay communications media; its sole intent is to restrict promotional claims of safety or effectiveness by the sponsor while the drug is under investigation to establish its safety or effectiveness.

(11) The sponsor shall not commercially distribute nor test-market the drug until a new-drug application is approved pursuant to section 505(b) of the the [sic] act.

(12) The sponsor shall obtain from each investigator involved in clinical pharmacology a signed statement in the following form:

Form FD 1572

Department of Health, Education, and Welfare,
Food and Drug Administration
Statement of Investigator
(Clinical Pharmacology)

Name of investigator _____

Date _____

Name of drug _____

To supplier of the drug:

Name _____

Address _____

Dear Sir:

The undersigned, _____, submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 130.3 of Title 21 of Code of Federal Regulations as a condition for receiving and conducting clinical pharmacology with a new drug limited by Federal (or United States) law to investigational use.

1. A statement of the education and training that qualifies me for clinical pharmacology.

2. The name and address of the medical school, hospital, or other research facility where the clinical pharmacology will be conducted.

3. The expert committees or panels responsible for approving the experimental project.

4. The estimated duration of the project, and the maximum number of subjects that will be involved.

5. A general outline of the project to be undertaken. (Modification is permitted on the basis of experience

gained without advance submission of amendments to the general outline.)

6. The undersigned understands that the following conditions generally applicable to new drugs for investigational use govern his receipt and use of this investigational drug:

a. The sponsor is required to supply the investigator with full information concerning the preclinical investigation that justifies clinical pharmacology.

b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantity, and use by subjects, and if the clinical pharmacology is suspended or terminated to return to the sponsor any unused supply of the drug.

c. The investigator is required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the clinical pharmacology.

d. The investigator is required to furnish his reports to the sponsor who is responsible for collecting and evaluating the results, and presenting progress reports to the Food and Drug Administration at appropriate intervals, not exceeding 1 year. Any adverse effects which may reasonably be regarded as caused by, or is probably caused by, the new drug shall be reported to the sponsor promptly; and if the adverse effect is alarming it shall be reported immediately. An adequate report of the clinical pharmacology should be furnished to the sponsor shortly after completion.

e. The investigator shall maintain the records of disposition of the drug and the case reports described above for a period of 2 years following the date of the new-drug application is approved for the drug; or if no application

is to be filed or is approved until 2 years after the investigation is discontinued and the Food and Drug Administration so notified. Upon the request of a scientifically trained and specifically authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The names of the subjects need not be divulged unless the records of the particular subjects require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual studies or do not represent actual results obtained.

f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him, _____, and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

g. The investigator certifies that he will inform any patients or any persons used as controls, of their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

Very truly yours,

_____

(Name of investigator)

_____

(Address)

_____

(13) The sponsor shall obtain from each investigator involved in clinical trials a signed statement in the following form:

Form FD 1573

Department of Health, Education, and Welfare, Food and Drug Administration

Statement of Investigator

Name of investigator_____
Date _____
Name of drug_____

To supplier of drug:
Name _____
Address _____

Dear Sir:

The undersigned, _____, submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical investigations with a new drug limited by Federal (or United States) law to investigational use.

1. The following is a statement of my education and experience:

a. Colleges, universities, and medical or other professional schools attended, with dates of attendance, degrees, and dates degrees were awarded.

b. Postgraduate medical or other professional training: Dates, names of institutions, and nature of training.

c. Teaching or research experience: Dates, institutions, brief description of experience.

d. Experience in medical practice or other professional experience: Dates, institutional affiliations, nature of practice, or other professional experience.

e. Representative list of pertinent medical or other scientific publications: Titles of articles, names of publications and volume, page number, and date.

(If this information has previously been submitted to the sponsor, it may be referred to and any additions made to bring it up to date.)

2. If any hospital, institutional, and clinical laboratory facilities, etc., are available and will be employed in conection [sic] with the investigation, an identification of each follows:

(If this information has previously been submitted to the sponsor, reference to the previous submission will be adequate.)

3. The investigational drug will be used by the undersigned or under his supervision in accordance with the plan of investigation described, as follows: (Outline the plan of investigation, including approximation of the number of subjects to be treated with drug and the number to be employed as controls, if any; clinical use to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be undertaken prior to, during, and after administration of the drug; the estimated duration of the investigation; and a description or copies of report forms to be used to maintain an adequate record of the observations and tests results obtained. This plan may include reasonable alternates and variations, and should be supplemented or amended when any significant change in direction or scope of the investigation is undertaken.)

4. The undersigned understands that the following conditions, generally applicable to new drugs for investigational use, govern his receipt and use of this investigational drug:

a. The sponsor is required to supply the investigator with full information concerning the preclinical investigations that justify clinical trials, together with fully informative material describing any prior investigations and experience and any possible hazards, contraindications, side-effects, and precautions to be taken into account in the course of the investigation.

b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantities, and use by subjects, and if the investigation is terminated to return to the sponsor any unused supply of the drug.

c. The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.

d. The investigator is required to furnish his reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained by various investigators. The sponsor is required to present progress reports to the Food and Drug Administration at appropriate intervals not exceeding 1 year. Any adverse effect that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if the adverse effect is alarming, it shall be reported immediately. An adequate report of the investigation should be furnished to the sponsor shortly after completion of the investigation.

e. The investigator shall maintain the records of disposition of the drug and the case histories described above for a period of 2 years following the date a new-drug application is approved for the drug; or if the application is not approved, until 2 years after the investigation is discontinued. Upon the request of a scientifically trained and properly authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The subjects' names need not be divulged unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual cases studied, or do not represent actual results obtained.

f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him, _____, and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

g. The investigator certifies that he will inform any subjects, including subjects used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

Very truly yours,

_____

(Name of investigator)

_____

(Address)

_____

(This form should be supplemented or amended from time to time if new subjects are added or if significant changes are made in the plan of investigation.)

(b) A shipment or other delivery of a new drug that is being imported or is offered for importation into the United States shall be exempt from the requirements of section 505(a) of the act if the following conditions are complied with:

(1) The label of such drug bears the statement "Caution: New drug—Limited by Federal (or United States) law to investigational use"; and

(2) The importer of all such shipments or deliveries is an agent of the foreign exporter residing in the United States or the ultimate consignee, which person has prior to such shipments and deliveries completed and submitted signed copies to the Food and Drug Administration of the "Notice of claimed investigational exemption for a new drug"; and acts as the sponsor of the clinical investigation to assure compliance with the conditions prescribed by paragraph (a) of this section; or

(3) The drug is shipped directly to a scientific institution with adequate facilities and qualified personnel to conduct clinical pharmacology and is intended solely for such use in such institutions and a "Notice of claimed investigational exemption for a new drug" covering this activity has been filed.

(c) Whenever a sponsor submits to the Commissioner the name of an investigator known to the Commissioner as having repeatedly or deliberately failed to comply with the conditions of these exempting regulations, the Commissioner will notify the sponsor that the investigator is not entitled to receive investigational-use drugs, and such investigator shall not be supplied any investigational-use

drug until adequate assurance is provided to and accepted by the Commissioner that the conditions of the exemption will be met. The Food and Drug Administration will be prepared to confer with the sponsor or the investigator, or both, on this point.

(d) If the Commissioner of Food and Drugs finds that:

(1) The submitted "Notice of claimed investigational exemption for a new drug" contains an untrue statement of a material fact or omits material information required by said notice; or

(2) The results of prior investigations made with the drug are inadequate to support a conclusion that it is reasonably safe to initiate or continue the intended clinical investigations with the drug; or

(3) There is substantial evidence to show that the drug is unsafe for the purposes and in the manner for which it is offered for investigational use; or

(4) There is convincing evidence that the drug is ineffective for the purposes for which it is offered for investigational use; or

(5) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug; or

(6) The plan for clinical investigations of the drugs described under section 10 of the "Notice of claimed investigational exemption for a new drug" is not a reasonable plan in whole or in part, solely for a bona fide scientific investigation to determine whether or not the drug is safe and effective for use; or

(7) The clinical investigations are not being conducted in accordance with the plan submitted in the "Notice of claimed investigational exemption for a new drug"; or

(8) The drug is not intended solely for investigational use, since it is being or is to be sold or otherwise distributed for commercial purposes not justified by the requirements of the investigation; or

(9) The labeling or other informational material submitted for the drug as required by section 7 of the "Notice of claimed investigational exemption for a new drug" or any other labeling of the drug disseminated within the United States by or on behalf of the sponsor fails to contain an accurate description of prior investigations or experience and their results pertinent to the safety and possible usefulness of the drug, including all relevant hazards, contraindications, side-effects, and precautions; or any promotional material disseminated within the United States by or on behalf of the sponsor contains any representation or suggestion that the drug is safe or that its usefulness has been established for the purposes for which it is offered for investigations; or

(10) The sponsor fails to submit accurate reports of the progress of the investigations with significant findings at intervals not exceeding 1 year; or

(11) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of newly found serious or potentially serious hazards, contraindications, side-effects, and precautions pertinent to the safety of the new drug;

he shall notify the sponsor and invite his immediate correction. A conference will be arranged if requested. If

the conditions of exemption are not immediately met, the Commissioner shall notify the sponsor of the termination of the exemption and the sponsor shall recall the unused supplies of the drug.

(e) Where drugs were under clinical trial on man on or after August 10, 1962, the sponsor shall, within 30 days after these regulations become effective, submit a list of such investigational drugs, and within 120 days after such effective date shall submit to the Food and Drug Administration the completed "Notice of claimed investigational exemption for a new drug" or a new-drug application. Failure to do so shall automatically terminate the exemption. If any such clinical trials have been discontinued, the sponsor is requested to submit a statement of why the investigation was discontinued.

(f)(1) A shipment or other delivery of a new drug for laboratory study or animal tests only shall be exempt from section 505(a) of the act if it is labeled: "Caution: New drug—Limited by Federal (or United States) law to laboratory studies and tests on animals. Not for human use." No animals used in such tests, or their products such as milk or eggs, shall be used for food purposes unless the sponsor or the investigator has submitted to the Commissioner data demonstrating that such use will be consistent with the public health, and the Commissioner, proceeding as he would in a matter involving section 409(i) of the act, has notified said sponsor or investigator that the proposed disposition for food purposes is authorized.

(2) The person or firm shipping a new drug for laboratory study or animals tests under this section shall use due diligence to assure that the consignee is regularly engaged in conducting laboratory studies or animal tests

and that the shipment of the new drug will actually be used for laboratory studies or animal testing.

(3) The person who introduced such shipment or who delivered the drug for introduction into interstate commerce maintains adequate records showing the name and post-office address of the expert to whom the drug is shipped, date, quantity, and batch or code mark of each shipment and delivery for a period of 2 years after such shipment and delivery. Upon the request of a properly authorized employee of the Department at reasonable times he makes such records available for inspection and copying.

(g) A "Notice of claimed investigational exemption for a new drug" which pertains to a product subject to the licensing provisions of the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended; 42 U. S. C. 201 et seq.) should be submitted initially to the Division of Biologics Standards, National Institutes of Health, Public Health Services, rather than to the Commissioner of Food and Drugs. Likewise, amendments of or supplements to such notice, and progress reports, consultations, or other communications with regard to the investigation, should be directed to the Division of Biologics Standards, which monitors the development of biological products subject to license under section 351 of the Public Health Service Act.

(h) Any requirement by this section for the submission of information or data that has been submitted previously may be incorporated by reference.

Effective date. This order shall become effective 30 days from the date of its publication in the Federal Register.